



Retrospective Analysis of Prognostic Value of Neutrophils to lymphocyte Ratio and Platelet Count in Patients with Colorectal Carcinoma

Thesis

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List of Abbreviations

<i>Abbr.</i>	<i>Full term</i>
CRC	Colorectal cancer
SEER	Surveillance, Epidemiology, and End Results
FAP	Familial Adenomatous Polyposis
LN	Lymph nodes
CAP	College of American pathologists
AJCC	American Joint Committee on Cancer
NLR	Neutrophil to lymphocyte ratio
GPS	Glasgow prognostic score
CRP	C-reactive protein
IL-6	Interleukin-6
SIR	Systemic inflammatory response
PLR	Platelet-lymphocyte ratio
COP-NLR	Combination of platelet count and neutrophil/lymphocytic ratio
OS	Overall survival
PFS	Progression-free survival
MMR	Mismatch repair
APC	Adenomatous polyposis coli
CK20	Cytokeratin 20
IHC	Immunohistochemistry
PD-1	Programmed cell death receptor 1

List of Abbreviations

NOS	Not otherwise specified
MSI	Microsatellite stability
IBD	Inflammatory bowel diseases
GI	Gastrointestinal
LDH	Lactate dehydrogenase
ALP	Alkaline phosphatase
CEA	Cancer Embryonic Antigen
EGFR	Epigrowth factor receptor
HNPCC	Hereditary nonpolyposis CRC [1])
CRM	Circumferential resection margin
VEGFR	Vascular endothelial growth factor receptor
mABs	Monoclonal antibodies
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
IRS1	Insulin receptor substrate 1

ABSTRACT

Background: Colorectal cancer (CRC) is the third most common cancer in men and second in women with 1.8 million new cases (1,026,000 men and 823, 3 women) and almost 881.000 deaths. Rates are substantially higher in males than in females Worldwide in 2018. **Aim of the work:** In this retrospective study we aimed to evaluate the prognostic impact of baseline NLR and platelet count on the clinicopathological factors and outcome in patients of all stages Colorectal cancer treated from 1st of January 2014 to the end of December 2016 in Department of Clinical Oncology and Nuclear Medicine, Ain Shams University hospitals, Cairo, Egypt. **Patients and methods:** Out of 409 patient's medical records in the GI oncology unit, Ain Shams Clinical Oncology Department were reviewed from the period between 1st of January 2014 to 30 December 2016. Total neutrophils, lymphocytic, and platelets' counts were available for only 169 patients. Study ended in 1st of August 2018 with median period of follow up of 27.5 month, ranging between 1/1/2014 to 1/8/2018. All patients (169) were pathologically proven colorectal adenocarcinoma, with age ranging from 18-75 years old (median age: 55.5 yrs.) **Results:** Out of 169 patients enrolled in this study, 124 patients were resectable and underwent curative surgeries, 44 patients tumour was right located and 80 patient's tumour located in the left sided colon. 45 patients were metastatic from the start. Postoperative Platelets ≥ 310 in our study was statistically significant regarding OS, PFS and DFS (P values $<.001$, $<.001$ and 0.007) respectively. Pre-treatment platelet revealed more frequent thrombocytosis in metastatic group than locally advanced group, yet statistically was not significant (P Value=.066). Postoperative NLR ≥ 2 was significant regarding OS, PFS and DFS among 169 enrolled patients (P values $<.001$, $.002$ and $<.001$) respectively. In the multivariate analysis, elevated postoperative NLR was proven as both independent prognostic and predictor factor for DFS, PFS and OAS. (sig. $=.03$, $.03$, ≤ 0.001 respectively). And platelet count is both independent prognostic factor and predictor for both PFS, OS with significance $=.04$, $=.03$ respectively). **Conclusion:** Abnormal NLR ratio (≥ 2) acting as a prognostic and predictor of decrease in DFS, PFS and OS in all patients groups. It also showed that abnormal platelet count (≥ 310) is prognostic and predictor of significant decrease in PFS and OS. Multidisciplinary management is needed to aware surgeons about importance of adequate lymph node dissection, our study showed a statistically significant decrease in OAS in patients underwent inadequate LNs dissection.

Key words: Neutrophils, lymphocyte, platelet Count, Colorectal Carcinoma

INTRODUCTION

Colorectal Cancer (CRC) is the third most common cancer worldwide and the fourth after breast, lung and prostate cancers in males, the 3rd in females according to latest Surveillance, Epidemiology, and End Results (SEER) data in United States (*SEER Cancer statistics, 2016*).

In 2017, about 95,520 new cases will be diagnosed with colon cancer in the United States and about 39,910 cases with rectal cancer (23,720 males and 16,190 females), and an estimated 27,150 men and 23,110 women will die from CRC in 2017 (*Siegel et al., 2017 and Miller et al., 2017*).

In Egypt, according to the Egypt National Cancer registry, the incidence rates/100,000 population of individual cancer sites are: in Upper Egypt in 2008 were 6.2 and 9.6, respectively; in Middle Egypt incidences were 6.7 and 9.7, respectively; while in Lower Egypt values were 8.0 and 10.7, respectively for both males and females (*Ibrahim et al., 2014*).

The relative survival rate for CRC is 65% at five years following diagnosis and 58% at ten years. Rectal cancer is diagnosed at a localized stage more than colon cancer (43% vs. 38%), likely due to the earlier appearance of symptoms (*American society of Cancer, 2017*).

Aside from age and race, many of the known risk factors for CRC including heredity and family history (30% of colorectal cancer is associated with family history and 5% with inherited syndromes such as Familial Adenomatous Polyposis (FAP), Attenuated FAP, and human non-polyposis colorectal cancer), chronic inflammatory bowel disease, overweight, diabetes, obesity, physical inactivity, smoking, alcohol use , low calcium, fiber and folate diet all are considered personal and behavioral risk factors for colorectal cancer (*Lutgens et al., 2013*) and (*Cho et al., 2004*).

Localized tumors that is confined to the primary site account for 39% of total cases (with five-year survival rate up to 90%), while regional involvement and distal metastasis at the time of diagnosis account for 35% and 25% respectively (accounts for five-year survival 71% and 13% respectively) (*SEER cancer statistics, 2016*).

Surgery is the main treatment modality in treating potentially curable cases aiming at complete removal of tumor with negative margins and involved lymph nodes (LNs). Adjuvant chemotherapy is standard for patients with stage III disease. Its use in stage II disease is controversial, with ongoing studies seeking to confirm which markers might identify patients who would benefit (*Dragovich et al., 2017*).

According to College of American pathologists (CAP) guidelines, factors that were determined to merit inclusion in Category I prognostic factors include: local extend of tumor according to American Joint Committee on Cancer (AJCC), regional Lymph nodes metastasis, residual tumor following surgery with curative intent and tumor grade (considered a stage independent prognostic variable) (*Compton et al., 2000*).

Factors in category II includes histological type and histological features associated with Microsatellite Instability (MSI) (*Compton et al., 2000*).

However, it's increasingly recognized that variations in outcome in cancer patients are not solely determined by

the characteristics of the tumor, but also by the host response factors and systemic inflammatory response (*Walsh et al., 2014*)

The tumor microenvironment, particularly the inflammatory response, proven to play an important role in in cancer development and progression (*Templeton et al., 2014*).

Over the last two decades, many studies on CRC have investigated host factors especially neutrophil to lymphocyte ratio (NLR) and platelet count as prognostic factors for local recurrence and survival. There is are a number of inflammation based prognostic systems like Glasgow prognostic score (GPS) which includes C-reactive protein (CRP) and hypoalbuminemia, increased NLR and thrombocytosis which are all based on cellular components that are regulated by cytokines especially interleukin-6 (IL-6) (*Ishizuka et al., 2013*).

Interleukin -6 is known to be multifunctional cytokine that acts on variety of cells, stimulates hepatocytes to induce acute phase proteins including CRP and decrease in serum albumin level (*Ramadori et al., 1998 and Ohsugi et al., 2007*).

It elicits not only neutrophils proliferation but also differentiation of megakaryocytes to platelets and their phenomena are also related to mechanism underlying host systemic inflammatory response (SIR). So, SIR can be assessed by examining the changes in the cellular components such as neutrophils, lymphocytes, monocytes, and platelets (*Ishizuka et al., 2013*)

Over the last 10 years, those laboratory markers of SIR have been investigated as prognostic factors in different cancer populations with the best evidence for their use in surgical patients with CRC (*McMillan et al., 2013*)

In 2007, **Leitch** and colleagues conducted a study comparing the prognostic value of selected markers of the systemic inflammatory response in 233 patients with colorectal cancer where the results supported the Modified GPS to be superior predictor of survival compared to cellular component of the systemic inflammatory response.

In 2010, **Ding** conducted a study investigating the elevated preoperative neutrophil to lymphocyte ratio in predicting risk of recurrence following curative resection for stage IIA colon cancer, study enrolled 141 patients from